ANTIMALARIAL DRUG TOXICITY: AN UPDATED BRIEF REVIEW

Noppadon Tangpukdee[1], Polrat Wilairatana[1,2], Shigeyuki Kano[3], Srivicha Krudsood[4]

[1]Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [2]WHO Collaborating Centre for Case Management, Training and Research on Malaria, Bangkok, Thailand; [3]Department of Tropical Medicine and Malaria, Research Institute, National Center for Global Health and Medicine (NCGM) Tokyo, Japan; [4]Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Abstract. Malaria, a serious infectious disease, continues to be a major health issue and a barrier to economic progress in many nations, particularly in tropical and subtropical areas. Apart from vector control and prevention strategies, at present, the creation of innovative antimalarial medications for prophylaxis or chemotherapy is the most promising approach to reducing malaria infection. Nevertheless, a number of antimalarial drugs have shown tolerability, safety and adequate therapeutic results for clinical management of malaria infection. Clinicians in different climatic regions, both temperate and tropical zones, may have different experiences towards malaria infection. In sub-tropics and tropics, clinicians are usually familiar with malaria and their main focus is on the effective treatment of malaria. However, malaria may be an uncommon disease in temperate zones. As a result, clinicians, therefore, will usually focus on prevention of malaria rather than treatment. Before prescribing a treatment regimen, a risk-benefit analysis must take into account the toxicity of antimalarial medications. A different outcome might occur in patients who are particularly susceptible, such as very young children, expectant or nursing mothers, or patients with clinically significant concomitant illnesses. At present, when the risk-benefit ratios of antimalarial drugs are still often controversial and imprecise, particularly among special risk groups. This review provides is an updated brief overview of the toxicity and adverse effects of current antimalarial drugs available in various parts of the world for both treatment and prevention.

Keywords: antimalarial, toxicity, review

Correspondence: Srivicha Krudsood, Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, 420/6 Ratchawithi Road, Bangkok 10400, Thailand
Tel: +66 (0) 2354 9159; Fax: +66 (0) 2354 9158 E-mail: srivicha.kru@mahidol.edu

INTRODUCTION

Malaria, the oldest known infectious disease, has been recognized as one of the most serious infectious diseases. According to six protozoan parasites in the genus *Plasmodium* that can infect humans, namely, *Plasmodium falciparum*, *P. knowlesi*, *P. malariae*, *P. vivax*, *P. ovale curtisi*, and *P. ovale wallikeri*, *P. vivax*, and *P. falciparum* predominate among malaria infections worldwide (WHO, 2022; Chemwor *et al*, 2023). Both malaria species are now responsible for the major causes of severe malaria and for the development of resistance to the present antimalarial drugs, resulting in declining treatment efficacy. Current epidemiological data indicate about half of the global population is at risk of malaria. Approximately 240 million malaria infections and up to 600,000 malaria fatalities are reported worldwide (WHO, 2022). The most serious concern is that deaths occur mostly among children in Africa, where a child dies from malaria every 60 seconds (WHO, 2022). Current approaches to reducing the spread of malaria include vector control, prophylaxis and prevention strategies, and effective chemotherapy (Alkadi, 2007).

Clinicians in different climatic zones may be experts with malaria but have different skills. Clinicians in the sub-tropical or tropical regions are usually familiar with malaria, since it is common and may cause significant regional mortality, thereby gaining experience in the clinical management of malaria. On the other hand, malaria may be an uncommon disease in temperate regions, where it is generally misdiagnosed. Temperate-region clinicians will usually focus on the prevention of malaria, and may not have the expertise in clinical treatment and management (Taylor and White, 2004).

It is well known that all available antimalarial drugs may cause toxicity or adverse effects (AEs). Toxicity is recognized as the hazardous degree of chemical agents or substances that can cause illness in humans or animals. AEs are known as any health abnormalities or life-threatening events that may be the results from

exposure to substances or chemical agents. Toxicity or AEs of antimalarial drugs are often observed when the recommended therapeutic dosage is increased. For example, taking a higher than the recommended dose of parenteral antimalarial drugs frequently causes damage to cardiac function and the neurological system (Luzzi and Peto, 1993).

TOXICITY OF CURRENT ANTIMALARIALS

Chloroquine

Chloroquine has been used to treat malaria for the past 60 years. The instance of fatal AEs to chloroquine is <1/100,000. This shows that chloroquine is relatively safe (Peto, 1989). It is still effective for the treatment and prophylaxis of *P. knowlesi*, *P. malariae*, *P. ovale*, and *P. vivax*, as well as drug-sensitive *P. falciparum*. Chloroquine is usually safe and well-tolerated, although it commonly produces mild AEs, such as pruritus, nausea, gastrointestinal upset, malaise, headache, dizziness, and difficulty in focusing. Africans or dark-skinned individuals experience generalized pruritus more frequently than African Canadians or Caucasians, which affects patient compliance (Mnyika and Kihamia, 1991). Chloroquine-induced pruritus is a complex interaction among drug, parasite and host. Moreover, associations between chloroquine-induced pruritus and hemoglobin genotypes and glucose-6-phosphate dehydrogenase (G6PD) variants have been described (Alkadi, 2007). A study in Thailand shows that only 1.9% of vivax malaria patients report mild to severe itching and respond favorably to antihistamine treatment (Bussaratid *et al*, 2000). Chloroquine may potentially affect eyesight, but the actual etiology of this AE has not been clearly explained (Peto, 1989). This might be the result of irreversible chloroquine binding with melanin and an extended period of use at high doses of the drug in rheumatoid arthritis patients may cause)are associated with high doses used for long periods in rheumatoid arthritis patients, rather than for malarial prophylaxis or treatment. Acute toxicity mostly occurs when chloroquine is administered intravenously at a higher-than-recommended dose. Parenteral administration of chloroquine frequently results in cardiovascular toxicity, including hypotension, cardiac depression and cardiac arrhythmia. Parenteral chloroquine was mentioned as a possible cause of death when administered at doses >5 g (Alkadi, 2007).

Chloroquine should be given either by infusion of <5 mg base/kg

for 4-6 hours or by subcutaneous or intramuscular injection of 3.5 mg base/kg every 6 hours to reduce the risk of adverse cardiovascular or neurological effects (White *et al*, 1988). Seizures have been associated with therapeutic doses and overdose of parenteral chloroquine. In overdose cases, seizures might occur within a few hours or several days after administration (Crawley *et al*, 2000). Chloroquine is also contraindicated in known cases of serious kidney or liver impairment, generalized psoriasis or epilepsy (Taylor and White, 2004; Alkadi, 2007). The use of chloroquine in pregnant or lactating women is now considered suitable in all three trimesters of pregnancy and for breastfeeding mothers (Ogunbona *et al*, 1987; Motta *et al*, 2002).

Primaquine

Primaquine, an 8-aminoquinoline, was introduced as a treatment for malaria more than 50 years ago. Primaquine is often used against liver schizont, liver hypnozoite and gametocyte stages of *P. ovale* and *P. vivax* to prevent the reappearance of malaria parasites. Primaquine can be taken after leaving transmission areas as a prophylactic agent. It has poor efficacy to kill asexual stages of *P. malariae*, *P. ovale*, and *P. vivax* (Pukrittayakamee *et al*, 1994), and is ineffective against the asexual stages of *P. falciparum* and *P. knowlesi* (van Schalkwyk *et al*, 2017). Therapeutic or higher doses of primaquine are recognized as a cause of hemolytic anemia, and sometimes fatal hemolysis in G6PD-deficient patients (Fraser and Vesell, 1968; Krudsood *et al*, 2008). The severity of hemolysis is commonly associated with the dosage and severity of G6PD deficiency status. Severity may be significantly augmented by certain co-existing diseases or when taken with other potential hemolysis agents such as sulfonamides (Sarkar *et al*, 1993). Due to differences in the sensitivity of liver stages of *P. vivax* to primaquine, the optimal dose for the treatment of "tolerant" or "resistant" strain are still debated (Taylor and White, 2004). Dosages as high as 22.5-30 mg/day have been suggested to achieve complete elimination of *P. ovale* and *P. vivax* (Wilairatana *et al*, 1999; Krudsood *et al*, 2008).

Primaquine is generally safe and tolerable when prescribed for the elimination of sexual-stage malaria parasites (*ie* as a gametocidal agent) and as a prophylactic agent administered daily with food (Taylor and White, 2004). Although the toxicity of primaquine to the gastrointestinal tract correlates with dosage, clinical presentations can improve if the drug is taken with food (Clayman *et al*, 1952). High doses are

likely to cause nausea, abdominal cramping, and sometimes vomiting and diarrhea (Taylor and White, 2004). The risk of granulocytopenia may increase when primaquine is administered to rheumatoid-arthritis patients (Brennecke *et al*, 1951). Cyanosis (methemoglobinemia) may occur with the recommended dose of primaquine. Cyanosis results from a dose-dependent oxidation of hemoglobin to methemoglobin by primaquine (Clayman *et al*, 1952). Although the incidence of methemoglobinemia is rare, patients with congenital deficiencies of nicotinamide adenine dinucleotide methemoglobin reductase may present with a severe condition. Methemoglobin is usually less pronounced in G6PD-deficient patients because older red blood cells tend to develop methemoglobin (Taylor and White, 2004). Other adverse events associated with primaquine include hypertension, arrhythmia, depression, and confusion. Pregnant and breastfeeding women should avoid taking primaquine because of the possibility of hemolysis in the mother and methemoglobinemia in the fetus. Because clinical information on primaquine in breast milk is very rare, it is also not recommended for lactating women (Taylor and White, 2004).

Mefloquine

Mefloquine, a quinolone methanol, is structurally similar to quinine. In recently years mefloquine is commonly prescribed for treatment and prophylaxis against malaria. Mefloquine is an effective against asexual-stage malaria parasites. If mefloquine is given in appropriate dose regimens, it is a very effective prophylactic agent (Ohrt *et al*, 1997). However, there have been reports of mefloquine-resistant *P. falciparum* in some areas of Southeast Asia and in the Amazon region (Cerutti *et al*, 1999; Nosten *et al*, 2000).

In general, mefloquine is safe and well-tolerated by patients. However, some reports have noted that mefloquine may cause higher rates of adverse events, such as dizziness, nausea, vomiting, fatigue, and insomnia than with other antimalarial drugs, such as chloroquine and artemether-lumefantrine (Van Vugt *et al*, 1998; Wilairatana *et al*, 1999). It may cause cardiac depressant effects, antifibrillary activity or marked adverse effects in the gastrointestinal or central nervous system (CNS). Significant clinical nausea, strange dreams (nightmares), psychosis, and sometimes even seizures, may occur after the administration of mefloquine. Mefloquine has a very long half-life; therefore, it is not

recommended as first-line treatment for malaria because of the increased frequency of AEs during the treatment regimens (Palmer *et al*, 1993). Serious CNS AEs, including seizures and hallucinations, have been reported in 1/10,000 individuals using mefloquine for malaria prophylaxis; subjects who develop severe CNS AEs are most likely to require hospitalization (Phillips-Howard and ter Kuile, 1995). AEs due to mefloquine are commonly observed when higher doses than recommended are administered (Phillips-Howard and ter Kuile, 1995). Mefloquine is cautioned in hypersensitive cases of severe psychiatric disorders, seizure disorder, epilepsy, and irregular heartbeat (Alkadi, 2007). In the cardiovascular system (CVS), mefloquine has been reported to cause sinus arrhythmia and aberrant atrioventricular conditions (Richter *et al*, 1997). Cutaneous toxicity after taking mefloquine is also mentioned. These AEs include pruritus, itching, rash, urticaria, cutaneous vasculitis, dermatitis, severe facial lesions, and Stevens-Johnson syndrome (Millard *et al*, 1999). Increases in serum transaminases have also been reported, but are rarely associated with hepatitis (Gotsman *et al*, 2000). For pregnant and breastfeeding women, mefloquine is effective and well-tolerated for both prophylaxis and treatment of malaria after the first trimester (Steketee *et al*, 1996). Prescribing mefloquine in the first trimester remains under careful review as its use most likely poses risks (Taylor and White, 2004). Prescribing mefloquine during lactation is still recommended as only small amounts are excreted in breast milk.

Amodiaquine

Amodiaquine, an analog of chloroquine, is the main treatment in African children with falciparum malaria, since it is inexpensive, easy to tolerate and does not taste as bitter as some other medications (White, 1996). Amodiaquine has not been recommended for malaria prophylaxis because of certain serious AEs. Serious hepatitis and agranulocytosis have been observed in some European travelers and individuals taking amodiaquine as prophylaxis (Larrey *et al*, 1986). Based on a study in Britain, the development risk of agranulocytosis is approximated as 1/2,200 and death in 1/31,300 cases. The risk of developing a serious hepatic complication is estimated to be 1/15,650 (Phillips-Howard and West, 1990). The number of events, however, depends on the national case reports of neutropenia and on the assessment of the frequency of UK prescriptions, resulting in an estimation of 1/2,000 cases.

Amodiaquine alone or in combination with artesunate for the treatment of acute uncomplicated falciparum malaria in African children shows high tolerability (Adjuik *et al*, 2002). Although clinical information and significance of decreasing neutrophil counts in some children are still undefined, the study results do not present severe hepatic or hematological reactions (Taylor and White, 2004). There is limited clinical information on using amodiaquine in pregnancy and lactating women (Moore and Davis, 2020).

Tafenoquine

Tafenoquine, a synthetic 8-aminoquinoline, was introduced as an alternative antimalarial drug for preventing vivax malaria relapses (Zottig *et al*, 2020). It was claimed that tafenoquine could be prescribed for the radical cure and prophylaxis of *P. ovale* and *P. vivax* malaria infections (Haston *et al*, 2019). A meta-analysis reports that a single dose (300 mg) of tafenoquine could reduce relapse in *P. vivax* patients compared with the standard dose of primaquine for the same indication (Rodrigo *et al*, 2020). A more recent study reports that tafenoquine, either treatment or prophylaxis, is generally well-tolerated in adult patients; however, tafenoquine is unlikely for use in pregnant or lactating women and patients with G6PD deficiency (Chu and Hwang, 2021). Further investigations of using tafenoquine in the field and in hospitals for radical cure and prophylaxis are urgently needed particularly in vulnerable subjects, *eg* G6PD-deficient patients, children, pregnant and lactating women (Rodrigo *et al*, 2020; Chu and Hwang, 2021).

Quinine

Quinine sulfate, a cinchona alkaloid, has been used for clinical management of both uncomplicated and complicated malaria infections for more than 300 years. It is also the secondary line agent for malaria treatment in the areas of drug-resistant *P. falciparum*, including Thailand. For uncomplicated falciparum malaria, quinine sulfate has to be administered for up to one week to achieve a radical cure. However, due to its bitter taste and unpleasant AEs, patients are often non-compliant. For severe malaria treatment, intravenous administration of quinine is recommended for rapid clearance of the malaria parasites. However, bolus intravenous injection of quinine has been shown to cause serious hypotension and sometimes cardiac arrhythmia (Taylor and White, 2004). AE in G6PD-deficient patients is hemolytic anemia (Alkadi, 2007). Quinine-induced thrombocytopenia is noted in Caucasians, although the

overall incidence rate is low (Freiman, 1990). Ototoxicity, including tinnitus and hearing loss, is reported as a toxic effect of quinine (Claessen *et al*, 1998). Permanent and transient blindness are reported in some malaria patients treated with quinine (Waddell, 1996). Toxicity of quinine is usually dose-dependent.

The standard recommended dose of quinine may cause cinchonism, hypoglycemia, hypotension, vasodilation, myocardial depression, and dysrhythmia (WHO, 2000). Although those unpleasant AEs frequently occur, AEs disappear soon after cessation of treatment (Alkadi, 2007). Hypoglycemia is a life-threatening AE, affecting 1/10 of severe malaria patients who are treated with parenteral quinine. This effect probably induces a quinine-mediated increase in the secretion of insulin (White *et al*, 1983). Approximately 50% of pregnant women, suffering from complicated malaria treated by quinine intravenously, exhibit hypoglycemia, resulting in difficulties in clinical management (Looareesuwan *et al*, 1985). Changes in behavior, tachypnea, convulsion, and coma may result from hypoglycemia and can also lead to misdiagnosis (WHO, 2000). Based on clinical evidence, it is noted that regimen doses of quinine are relatively safe for pregnant women but patients should be closely monitored for signs of hypoglycemia (McGready *et al*, 2002). In lactating women, 30% of the maternal quinine dosage can be excreted into breast milk and also cross into the placenta. However, therapeutic doses of quinine are still recommended for clinical management during pregnancy and breastfeeding (Taylor and White, 2004).

Sulfadoxine/Pyrimethamine

Fansidar®, a combination of sulfadoxine and pyrimethamine, was useful in antimalarial combination therapy in Thailand before parasite drug resistance made it less effective (Looareesuwan *et al*, 1992). Based on AEs, Fansidar® is not recommended for malaria prophylaxis (Alkadi, 2007). Serious AEs, such as Steven-Johnson syndrome, were observed (Phillips-Howard and West, 1990). Sulfadoxine/pyrimethamine may also cause liver complications, including acute hepatic necrosis, mixed cholestatic-hepatocellular hepatitis, liver granulomas, and chronic hepatitis (Wejstal *et al*, 1986). Excessive doses may lead to megaloblastic anemia, similar to folate deficiency observed in response to treatment or withdrawal of folic acid. This effect may result in severe conditions in vulnerable patients, *eg* children suffering from malnutrition and pregnant women

(Taylor and White, 2004). There is little clinical information on the use of sulfadoxine/pyrimethamine during the 1st trimester of pregnancy. In areas where sulfadoxine/pyrimethamine remains effective, it plays a significant role in clinical malaria management, particularly prevention of malaria during pregnancy in hyperendemic areas where low-birth weight of babies and maternal anemia are serious problems (Taylor and White, 2004). During lactation, sulfadoxine/pyrimethamine may be excreted into breast milk. However, monitoring treatment of sulfadoxine/pyrimethamine during breastfeeding among Malawi women shows that it is well-tolerated in both mothers and babies (Taylor and White, 2004), although more information is needed. Sulfadoxine/pyrimethamine is still prescribed to African women who are breastfeeding, and mothers who receive this medication should be warned of its potential toxicity and adverse events (Saito *et al*, 2018).

Halofantrine

Halofantrine, a phenanthrene methanol, is a potential agent for the clinical management of chloroquine resistance in both *P. falciparum* and *P. vivax* (Fryauff *et al*, 1997). However, halofantrine has several drawbacks in the treatment of malaria, *eg* poor drug absorption, cross-resistance to mefloquine and a high rate of treatment failure. Halofantrine, therefore, has not been recommended for the first line treatment or in the prevention of malaria (WHO, 2012). AEs, such as abdominal pain, diarrhea, vomiting, headache, rash, itching, and elevated serum transaminases might result from halofantrine treatment. Cardiotoxicity may also be associated with the standard treatment regimen of halofantrine and cardiac arrhythmia is a serious side effect (Wesche *et al*, 2000). Halofantrine should therefore not be prescribed to patients with cardio-function defects, *eg* prolonged QTc interval, and should not be used in combination with mefloquine. However, a study by Bouchaud *et al* (2009) concludes that halofantrine is safe and well tolerated when appropriately administered, but administration of halofantrine during pregnancy and breastfeeding is not recommended, as clinical data on these situations are insufficient.

Atovaquone/Proguanil

Atovaquone/proguanil is a combination antimalarial agent for malaria management, both prophylaxis and treatment, as atovaquone alone is not effective. This drug combination is commercially available under the trade name of Malarone® or Malanil®. Clinical safety data of atovaquone/proguanil

have shown that it is safe and well-tolerated (Krudsood *et al*, 2007). Most AEs reported are related to malaria itself rather than the drug (Taylor and White, 2004). The major symptoms are mild, namely, anorexia, diarrhea, vomiting, nausea, abdominal pain, neutropenia, anemia, hyponatremia, coughing, dizziness, headache, insomnia, fever, rash, and increased serum transaminases. Clinical studies of prophylactic atovaquone/proguanil in travelers show it to be well-tolerated compared with chloroquine-proguanil or mefloquine (Høgh *et al*, 2000; Savelkoel *et al*, 2018). Serious toxicity after taking atovaquone/proguanil has rarely been recorded; however, anaphylaxis or pustulosis was observed in some clinical studies (Looareesuwan, *et al*, 1999; Arsuaga *et al*, 2020). Use of atovaquone/proguanil in pregnant women should only be considered if no other more appropriate regimen of an antimalarial agent is available. Before administering atovaquone/proguanil in breast-feeding women, they should be advised regarding the possible AEs (WHO, 2012).

Artemisinin and derivatives

Artemisinin ("qinghaosu") was initially discovered in the 1970s by Chinese researchers who characterized the antimalarial property of the traditional Chinese medical drug "qinghao" (the blue-green herb) and showed its excellent safety and tolerability (Anonymous, 1982). Previously many artemisinin derivatives, such as arteether, artemether, artesunate, and dihydroartemisinin were shown to have good therapeutic effects against malaria (Krudsood *et al*, 2003; Silachamroon *et al*, 2003; Tangpukdee *et al*, 2005; Tangpukdee *et al*, 2008a). Artemisinin derivatives have been used in combination with other antimalarial drugs to obtain synergistic effects. Artemisinin combination therapies (ACTs) are currently used as the first-line regimen for the clinical management of malaria in many endemic regions, including Thailand (WHO, 2023). A review of publications on artemisinin derivatives, which were previously conducted by Chinese scientists, reported that artemisinin derivatives had no serious adverse drug reactions and had excellent tolerability (Ribeiro and Olliaro, 1998). Reported AEs depend on the type of artemisinin analogues and route of administration. Hematological changes, such as low percent neutrophil, decreased reticulocyte count, anemia, thrombocytopenia, increased percent eosinophil, and raised aspartate aminotransferase level, have been reported (Tangpukdee *et al*, 2006; Tangpukdee *et al*, 2008b;

Leowattana *et al*, 2010). In addition, a post-artemisinin delayed hemolysis has been observed (Rehman *et al*, 2014). Electrocardiogram (ECG) abnormalities without clinical signs, such as transient bradycardia, prolonged QTc interval and prolongation of PR interval as well as change in nonspecific T wave, are observed in some patients (Krudsood *et al*, 2011). A number of patients present allergic reactions after receiving oral artesunate alone; the estimated risk for this serious event is 1/2,833 (Leonardi *et al*, 2001). Artemisinin derivatives can cause neurotoxicity. Taylor and White (2004) documented cases in animal models of the neurotoxic effects associated with artemisinin derivatives, which may also occur in humans. In clinical studies, neurotoxic effects have been observed in some patients. Miller and Panosian (1997) noted acute cerebral dysfunction, including ataxia and slurred speech, in one falciparum patient receiving oral artemisinin. On the other hand, two clinical studies in Thailand and Vietnam reported that there are no consistencies between neurotoxic complications and treatment with artemisinin derivatives (Kissinger *et al*, 2000; Van Vugt *et al*, 2000).

According to recently published data, a short-course therapy of ACTs is still recommended to treat malaria in many areas (WHO, 2022). There are currently no details regarding the overdose toxicity of artemisinin. However, overdose patients should be managed and closely monitored for system in the cardiovascular and central nervous systems (Bond, 2006). There is limited clinical information on the administration of artemisinin derivatives during the first trimester of pregnancy (McGready *et al*, 2012; WHO, 2022). Animal studies showed that artemisinin and its derivatives might interrupt erythropoiesis of the fetus, resulting in fetal resorption (D'Alessandro *et al*, 2020). However, WHO endorsement of the administration of artemisinin analogues in the first trimester is anticipated. However, artemisinin derivatives are safe during the second and third trimesters of pregnancy (UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases & The Global Malaria Programme, 2007; WHO, 2015).

Artemether/Lumefantrine

Artemether/lumefantrine is an artemisinin combination therapy (ACT) for treating acute uncomplicated *P. falciparum* malaria. It is a combination of the rapid-acting artemether with a long-acting lumefantrine. This drug is commercially available

under the trade name Coartem® or Riamet®. Artemether/lumefantrine is an effective agent against *P. falciparum* and *P. vivax* infections but its hypnozoitocidal action remains unclear (Bassat, 2011). Artemether/lumefantrine is safe and well-tolerated in all age groups (Kamugisha *et al*, 2012). Most AEs reported range from mild to moderate and are probably associated with malaria itself rather than the drug (Carrasquilla *et al*, 2012). Confounding factors are also likely to be the causes of AEs, such as co-infection or co-administration of other medicines, but details on the exact nature of the confounding factors remain inconclusive (Carrasquilla *et al*, 2012; Kamugisha *et al*, 2012). In safety study analyses, mood swings are recorded in <1.2% of pediatric patients after treatment with artemether/lumefantrine, but the events are considered not to be associated with the product. AEs reported in non-recommended regimens are not included in the safety analysis, such as involuntary muscle contractions (in ~1.3% of children) and paresthesia (none in children, but 1.2% in adolescents and adults). Thus, electrolyte imbalance and abnormal heart function should be closely monitored (Novartis Pharmaceuticals, 2023). Artemether/lumefantrine is not recommended during the first trimester of pregnancy; however, in the second and the third trimesters, treatment may be prescribed upon taking into consideration the risks and benefits to mother and fetus (Piola *et al*, 2010; Manyando *et al*, 2015). Because of the long half-life of lumefantrine, it is suggested that breastfeeding be permitted at least 4 weeks post-treatment unless the potential benefits to mother and child outweigh the risks of the medication, but further studies are needed on artemether/lumefantrine treatment during pregnancy. However, in the event of a lack of other more appropriate antimalarials clinicians may prescribe (taking into consideration the possible side effects) artemether/lumefantrine for treating malaria, particularly in areas of multidrug-resistant falciparum malaria (Taylor and White, 2004).

Dihydroartemisinin/Piperaquine

Dihydroartemisinin/piperaquine, an ACT, has been approved for use in the European Union and introduced for use as an antimalarial drug for many decades. At present, several forms of fixed-dose formulations are available. Dihydroartemisinin/piperaquine has good efficacy in the clinical management of uncomplicated falciparum malaria (Tangpukdee *et al*, 2005; Tangpukdee *et al*, 2008a; Keating, 2012). However, there is limited clinical information on the usage

of dihydroartemisinin/piperaquine in infants <6 months of age or with a body weight <5 kg (European Medicines Agency, 2021). AEs of this combination drug are generally mild to severe but temporary and with good tolerability. However, prescribing dihydroartemisinin/piperaquine should be considered with care and particular attention paid to the elderly and to patients with liver or kidney dysfunction (European Medicines Agency, 2021). There was a report of choreoathetosis as an uncommon AE of dihydroartemisinin/piperaquine treatment (Kadia *et al*, 2017). An assessment by the European Union (EU) reported that, although some patients have no symptoms of torsade de pointes, QTc prolongation, ventricular tachycardia, ventricular flutter, or ventricular fibrillation are presented after treatment (European Medicines Agency, 2021). A meta-analysis shows a low risk of sudden unexplained cardiac arrest associated with dihydroartemisinin/piperaquine treatment (Chan *et al*, 2018), which could be reduced by administration in a fasting state if there is concern of sudden death or risk of torsade de pointes in patients with prolonged QT/QTc interval (Funck-Brentano *et al*, 2019). There is limited information on the use of the medication in pregnant women (Keating, 2012). Further studies are needed on cardiac toxicity in dihydroartemisinin/piperaquine treatment of uncomplicated falciparum malaria before recommendation of its application in the field.

Artesunate/Pyronaridine

Pyronaridine/artesunate (Pyramax®), an ACT, is used for the clinical management of uncomplicated malaria, both *P. falciparum* and *P. vivax*. This ACT is available as tablets and as granules for use in adults and pediatric patients with a body weight between 5-20 kg (European Medicines Agency, 2022). The use of pyronaridine/artesunate at a country level was recently supported by WHO (2021). Pyronaridine/artesunate is well tolerated for clinical management of uncomplicated malaria (Leang *et al*, 2019; Tona Lutete *et al*, 2021; Stone *et al*, 2022). The most common AEs (1-10%) are headache, and abnormalities in platelet, red blood cell and white blood cell counts, liver function profile, and blood sugar. Hepatotoxicity and renal toxicity concerns were advised for consideration when recommended for general use (WHO, 2019). Further information on the use pyronaridine/artesunate, particularly in vulnerable patients, *eg* pregnancy, lactating women, and immunocompromised patients, are awaited to clarify risk and benefits.

RECOMMENDATION

Most of the antimalarial drugs are generally safe. The incidence of serious AEs is very low, the common being liver and kidney injury, *eg* in Amodiaquine, Sulfadoxine/Pyrimethamine and Pyronaridine/Artesunate medication; therefore, these antimalarials should be prescribed with caution to patients with known underlying diseases. In addition, hematological abnormalities have been reported in the use of Amodiaquine. However, Chloroquine and Artemether/Lumefantrine are generally safe and well-tolerated for pregnant and lactating women in all age groups. Regarding the 8-aminoquinoline anti-hypnozoitecidal drugs, *eg* Primaquine and Tafenoquine, prescribing to G6PD deficient individuals poses risk of acute hemolysis. In areas where a G6PD test is not available, close monitoring of signs and symptoms of anemia is recommended.

Malaria prevention strategies must carefully take into consideration the risks and benefits of antimalarial drugs, particularly as prophylactic agents, before recommending them to travelers, *ie* risk of the potential serious AEs versus effective protection from malaria. The risk of malaria in tourists who are visiting endemic areas for extended durations should out-weigh that of short-term tourists. In addition, travelers who visit areas of low malaria transmission would be at a much lower comparative risk. Thus, the decision whether to prescribe antimalarial prophylaxis, depends on the requirements of the traveler. However, all available antimalarial drugs, including those prescribed for treatment and prophylaxis, have common AEs. For an adequate clinical response, however, it should be noted that toxicity risk may be low but with severity ranging from mild to moderate to severe and sometimes to life-threatening (Croft *et al*, 2002)

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